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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,179	03/11/2002	Jeffrey Errington	HO-P02222US0	2178

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EXAMINER	
SCHLAPKOHL, WALTER	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,179	ERRINGTON, JEFFREY	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	mdj

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/14/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed 11/4/2005 and on 11/14/2005 in which claims 31-36 were canceled.

Election/Restrictions

Applicant's election of Group I (claims 19-30) in the reply filed on 11/4/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The restriction is still deemed proper and therefore made FINAL.

Priority

Receipt is acknowledged of papers filed under 35 U.S.C. 119 (a)-(d) based on an application filed in the European Patent Office on 12/22/1998. Applicant has not complied with the requirements of 37 CFR 1.63(c), since the oath, declaration or application data sheet does not acknowledge the filing of any foreign application. A new oath, declaration or application data sheet is required in the body of which the present

application should be identified by application number and filing date.

The foreign priority claim filed on 3/11/2002 was not entered because the foreign priority claim was not filed during the time period set forth in 37 CFR 1.55(a)(1). For original applications filed under 35 U.S.C. 111(a) (other than a design application) on or after November 29, 2000, the time period is during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior foreign application. For applications that have entered national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the claim for priority must be made during the pendency of the application and within the time limit set forth in the PCT and the Regulations under the PCT. See 37 CFR 1.55(a)(1)(ii). If applicant desires priority under 35 U.S.C. 119(a)-(d), (f) or 365(a) based upon a prior foreign application, applicant must file a petition for an unintentionally delayed priority claim (37 CFR 1.55(c)). The petition must be accompanied by (1) the claim (i.e., the claim required by 35 U.S.C. 119(a)-(d) and (f) and 37 CFR 1.55) for priority to the prior foreign application, unless previously submitted; (2) a surcharge under 37 CFR 1.17(t); and (3) a

statement that the entire delay between the date the claim was due under 37 CFR 1.55(a)(1) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Specification

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-20, 26 & 30, and therefore dependent claims 21-25 and 27-29, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and

distinctly claim the subject matter which applicant regards as the invention.

Claim 19 recites "[a] method for identifying a regulatory sequence which is affected by a feedback mechanism on alteration of synthesis or activity of a bacterial essential protein" in lines 1-2. Claim 19 is vague and indefinite in that the metes and bounds of "bacterial essential protein" are unclear. For example, must the protein be essential to the viability of a particular bacterium or does "bacterial essential protein" encompass any protein of known or unknown function whose expression *in vivo* is subject to a feedback mechanism?

Claim 20 recites "[a] method for identifying a regulatory sequence whose activity is affected by a feedback mechanism or an alteration of the synthesis or activity of an essential bacterial protein" in lines 1-3. Claim 20 is vague and indefinite in that the metes and bounds of "an essential bacterial protein" are unclear. For example, must the protein be essential to the viability of a particular bacterium or does "an essential bacterial protein" encompass any protein of known or unknown function whose expression *in vivo* is subject to a feedback mechanism?

Claim 26 recites "[t]he method of claim 23, wherein the regulatory sequence has the activity of a promoter for the

nucleic acid sequence encoding the essential protein and inhibition of the essential protein up-regulates expression from its promoter" in lines 1-3. Claim 26 is vague and indefinite in that it is not clear which promoter is referred to by "its promoter" in line 3: is it the promoter of the regulatory sequence operably linked to a reporter nucleic acid, the promoter of the essential protein or both?

Claim 30 recites "[t]he method of claim 23, further comprising determining whether the test substance demonstrates specific inhibition of the essential protein" in lines 1-2. Claim 30 is vague and indefinite in that it is unclear whether the test substance need inhibit the essential protein being tested at the exclusion of other essential proteins or whether "specific inhibition of the essential protein" refers to down-regulation of the essential protein via direct inhibition/repression of its regulatory sequence and not as a result of a feedback mechanism.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-25 and 27-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods comprising the use of a candidate regulatory sequence *from a bacterial essential protein* operably linked to a reporter gene, does not reasonably provide enablement for *any* candidate regulatory sequence operably linked to a reporter gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with the most relevant factors discussed below.

Nature of the invention: The rejected claims are drawn to methods of identifying a regulatory sequence which is affected by a feedback mechanism on alteration of sysnthesis or activity of a bacterial essential protein, comprising: i) providing a bacterial cell having a reporter gene under the control of a

candidate regulatory sequence, ii) selecting a target essential protein which is expressed in the cell, iii) altering the synthesis or activity of the essential protein, iv) monitoring expression of the reporter gene, and v) determining thereby whether the candidate regulatory sequence is affected by a feedback mechanism responsive to alteration of the synthesis or activity of the essential protein. The rejected claims are also drawn to methods of identifying regulatory sequences affected by a feedback mechanism comprising : a) monitoring expression of a bacterial gene in a bacterial host cells in the presence of normal and altered synthesis or activity of the essential protein, b) identifying differential gene expression in the presence of normal and altered synthesis or activity of the essential protein, and c) identifying thereby a regulatory sequence whose activity is affected by the feedback mechanism. The invention is further drawn to methods for identifying a modulator of a bacterial essential protein utilizing a regulatory sequence identified by the methods of claim 19 recited above.

The invention is complex in that it involves an interplay between the synthesis or activity a protein essential to a bacterium and whatever factors are included in a feedback circuit involving the bacterial essential protein and its effect

on a candidate regulatory sequence operably linked to a reporter nucleic acid. Compounds or constructs must be used to alter the synthesis or activity of the bacterial essential protein in such a way as to allow the maintenance of viability of the bacterium until such time as the feedback effect can be monitored by changes in reporter gene expression or differences in gene expression between bacteria in the presence of normal and altered synthesis or activity of the essential protein. The invention must also be able to discriminate between test substances which affect the activity or synthesis of the essential protein and do NOT affect the activity of candidate regulatory sequences directly since such substances would provide either false positive or false negative results with respect to their ability to affect a feedback mechanism on alteration of synthesis or activity of a bacterial essential protein. In other words, the method of altering the bacterial essential protein cannot also *directly* act to, for example, increase the expression of the reporter gene, because in such a case the increase in expression of the reporter gene would not be indicative of a feedback mechanism.

Upon identification of the regulatory sequences which are affected by a feedback mechanism on alteration of synthesis or activity of a bacterial essential protein, the regulatory

sequences would be used to identify modulators of bacterial essential proteins themselves by monitoring differences in the expression of a reporter gene. Since the method of identification of such sequences is not enabled for candidate regulatory sequences other than regulatory sequences of bacterial essential proteins themselves, further methods involving the use of such identified regulatory sequences are also not enabled beyond the scope of the method claim from which they depend.

Breadth of the claims. The claims are very broad in that they encompass the use of any bacterial essential protein, any candidate regulatory sequence operably linked to any reporter gene. As mentioned above, the specification, while being enabling for methods comprising the use of a candidate regulatory sequence *from a bacterial essential protein* operably linked to a reporter gene, does not reasonably provide enablement for any candidate regulatory sequence operably linked to a reporter gene. For example, if one of ordinary skill in the art were to practice this invention using luciferase as a reporter gene under the control of a cytomegalovirus (CMV) constitutive promoter as a candidate regulatory sequence and then inhibited the activity of RNA polymerase (a bacterial essential protein), how would expression of the reporter gene

determine whether the candidate regulatory sequence is affected by a feedback mechanism on the alteration in synthesis or activity of a bacterial essential protein? Wouldn't such a change instead be indicative of a general lack of gene expression and NOT a feedback mechanism? What if the targeted bacterial essential protein in this system were instead a D-alanine racemase? Could inhibition of such a target gene (responsible for converting L-alanine to D-alanine) result in a detectable change in luciferase activity resulting from a feedback mechanism on the altered D-alanine racemase activity? Absent evidence to the contrary, the only candidate regulatory sequences enabled for the claimed methods are regulatory sequences for the bacterial essential proteins themselves, which may or may not be susceptible to changes in activity or expression of their operably linked essential proteins and thus identified on the basis of such a feedback regulatory mechanism.

Guidance provided by the specification/The existence of working examples: Applicant has provided only one working example of a method for identifying a regulatory sequence which is affected by a feedback mechanism on alteration of synthesis or activity of a bacterial essential protein comprising the steps recited above. The specification describes two *Bacillus subtilis* strains containing the *gyrA* (bacterial essential) gene

under the control of a P_{spac} promoter and a *lacZ* reporter gene under the control of the natural promoter for *gyrA*. The *B. subtilis* strain is then grown in the absence of IPTG, which is known to decrease expression of DNA gyrase from the P_{spac} promoter. Growth in the absence of IPTG also leads to increased beta-galactosidase expression, "indicating that the promoter is subject to negative feedback regulation" (see instant specification, page 20, lines 1-17). Even assuming that the increase in beta-galactosidase expression is not spurious or indicative of some other IPTG-related regulatory mechanism, identification of the regulatory sequence as "affected by a feedback mechanism responsive to alteration of synthesis or activity of a bacterial essential protein" would not be possible for candidate regulatory sequences other than those sequences known to be in the feedback circuit (i.e. that of the bacterial essential protein itself and, possibly, those proteins with which the bacterial essential protein interacts in essential bacterial processes).

Working examples in the literature: Neumann et al teach an example of such a method for identifying a regulatory sequence which is affected by a feedback mechanism on alteration of synthesis or activity of a bacterial essential protein (J. Basic Microbiol. 37(1):53-69, 1997). Neumann et al do not describe

such a method wherein any regulatory sequence is combined with any reporter gene. Rather, Neumann et al describe such a method wherein the regulatory sequence from two bacterial essential proteins (gyrase A and gryase B) are operably linked to a lacZ reporter gene. No other working examples involving promoters other than those with the activity of the associated essential bacterial protein are evident in the literature.

Predictability in the art: Methods for combining various regulatory sequences with any given reporter molecule to determine which regulatory sequences are affected by a feedback mechanism involving a bacterial essential protein are scarce in the art and unpredictable. In a review article published concurrent with application EPO 98310567.7, to which the instant application claims priority, Aileen Allsop notes that the use of expression profiling for functional analysis is at an early stage (Current Opinion in Biotechnology 9:637-642; IDS Ref. CA; see entire document, especially page 639, second column, second paragraph) and that the desire to identify genes associated with pathogenic processes has resulted in the development of at least three different approaches: the identification of genes specifically induced during an infection, the uncoupling of metabolic requirements from selection parameters, and the identification of genes by mutation for the establishment and

maintenance of infection (p. 639, first column, last two paragraphs). No description is provided, nor is mention made of technologies based around gene expression changes involving feedback mechanisms that affect the synthesis or activity of bacterial essential proteins.

Amount of experimentation necessary: Given the unpredictability of the art, the lack of guidance provided by the specification regarding which candidate regulatory sequences to test and how to couple such regulatory sequences to reporter molecules such that a change in expression would be indicative of a feedback mechanism that affects the synthesis or activity of a bacterial essential protein, a great deal of experimentation would be required to reduce the full scope of Applicant's invention to practice. The fact that these identified regulatory elements would then be used in further methods for identifying modulators of bacterial essential proteins adds further complexity to the invention for which the prior art provides only scarce examples, those being methods wherein the regulatory sequences tested are those associated with the endogenous bacterial essential protein(s).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods for identifying a modulator of a bacterial essential protein comprising the step of providing a bacterial host cell which expresses the essential protein and wherein the cell comprises a polynucleotide construct comprising a regulatory sequence operably linked to a reporter nucleic acid, wherein the regulatory sequence is associated with a feedback mechanism responsive to alteration in the synthesis or activity of the essential protein and identified according to the method of claim 19. The claims encompass any regulatory sequence associated with a feedback

mechanism responsive to a change in synthesis or alteration of a bacterial essential protein operably linked to any reporter gene. The claims do not provide any structural information with regard to the regulatory sequences responsive to alterations in the synthesis or activity of an essential protein. Thus, the rejected claims comprise a set of nucleic acid sequences that are defined by their function. The claims are further encompass methods for identifying a modulator of any kind for any bacterial essential protein wherein the modulator is identified in the method of claim 19. The claims do not provide any structural information regarding candidate modulators or bacterial essential proteins or any information with regard to their mechanism of action.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification refers to one candidate regulatory sequence specifically: "the natural promoter for *gyrA*" which is operably linked to the *lacZ* reporter gene (p. 20, lines 12-17). The specification also

describes contacting a test substance to a bacterial host cell which expresses a bacterial essential protein and comprises this *gyrA-lacZ* construct and monitoring expression of the reporter gene to determine thereby whether said substance modulates the synthesis or activity of the essential protein. No other examples of regulatory sequences are provided and no sequence information or structure is provided, either for the *gyrA* promoter or any other regulatory sequence. Regarding modulators of bacterial essential proteins identified by the method of claims 23-30, the specification describes two compounds, proflavine and trimethoprim, that "registered as positives" in the screening assay performed, i.e. increased beta-galactosidase activity from the reporter gene with a gyrA promoter (page 21, lines 7-15). However, the specification does not describe these as modulators of a bacterial essential protein and further notes that these compounds are known to affect other aspects of DNA metabolism (ibid). Applicant concludes therefrom that the feedback regulation exploited with the assay strain *should* be useful in identifying inhibitors of DNA gyrase and possibly compounds acting on other facets of the DNA replication machinery. Thus, the specification does not describe a single example of a modulator of a bacterial essential protein identified by such a method.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of one nucleic acid sequence identified by the method of claim 19 and two potential modulators of a single bacterial essential protein. The results are not necessarily predictive of any other regulatory sequences associated with a feedback mechanism responsive to alteration in the synthesis or activity of the essential protein and identified according to the method of claim 19. Neither are the results predictive of other candidate modulators that might be identified. Thus it is impossible to extrapolate from the example described herein those nucleic acid molecules and candidate modulators identified therefore that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of nucleic acids identified in a method for identifying regulatory sequences affected by a feedback mechanism on alteration of synthesis or activity of bacterial essential protein that are anything other than regulatory sequences for proteins required for essential bacterial functions such a DNA synthesis. Neumann et al (see reference above) describe the identification of two

regulatory sequences for gyrases A and B in such a method and then utilize those sequences to screen known gyrase inhibitors for changes in gyrase A and B expression. The "essential bacterial protein modulators" that Neumann et al use in their screening method were thus already were known to inhibit gyrases generally and the effect of such modulation was explored in terms of the difference in expression achieved between regulatory sequences of gyrase A and gyrase B by such inhibitors.

Given the very large genus of nucleic acid molecules encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the regulatory sequences capable of fulfilling the claim limitations of claims 23-30, the skilled artisan would not have been able to describe the broadly claimed genus of regulatory sequences operably linked to a reporter nucleic acid, wherein the regulatory sequence is associated with a feedback mechanism responsive to alteration in the synthesis or activity of the essential protein and identified according to the method of claim 19. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those nucleic acid sequences that satisfy the functional limitations of the claims. Therefore,

the skilled artisan would have reasonably concluded Applicant was not in possession of the claimed invention for claims 23-30.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19-20 and 23-26, 28 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Neumann et al (J. Basic Microbiol. 37 (1):53-69, 1997).

Applicant's invention is drawn to a method for identifying a regulatory sequence which is affected by a feedback mechanism on alteration of synthesis or activity of a bacterial essential protein, comprising: i) providing a target essential protein which is expressed in the cell, ii) selecting a target essential protein which is expressed in the cell, iii) altering the synthesis or activity of the essential protein, iv) monitoring expression of the reporter gene, and v) determining thereby whether the candidate regulatory sequence is affected by a feedback mechanism responsive to alteration of the synthesis or

activity of the essential protein (claim 19). Applicant's invention is further drawn to a method of identifying a regulatory sequence whose activity is affected by a feedback mechanism or an alteration of the synthesis or activity of an essential bacterial protein, comprising: (a) monitoring expression of a bacterial gene in a bacterial host cell in the presence of normal and altered synthesis or activity of the essential protein; (b) identifying differential gene expression in the presence of normal and altered synthesis or activity of the essential protein; and (c) identifying thereby a regulatory sequence whose activity is affected by the feedback mechanism (claim 20). The invention is further drawn to a method for identifying a modulator of a bacterial essential protein, comprising i) providing a bacterial host cell which expresses the essential protein, wherein the cell comprises a polynucleotide construct comprising a regulatory sequence operably linked to a reporter molecule, wherein the regulatory sequence is associated with a feedback mechanism responsive to alteration in the synthesis or activity of the essential protein; ii) contacting a test substance with the host cell; and iii) monitoring expression of the reporter gene to determine thereby whether said substance modulates the synthesis or activity of the essential protein (claim 23). The invention is

further drawn to such a method wherein the essential protein is involved in cell wall synthesis, teichoic acid synthesis, DNA replication, RNA synthesis, cell division, chromosome segregation, translation or lipid synthesis (claim 24) and wherein the inhibition of the essential protein up-regulates expression of the reporter nucleic acid sequence from the regulatory sequence.

Neumann et al teach a method of identifying a regulatory sequence which is affected by a feedback mechanism on alteration of synthesis or activity of a bacterial essential protein. Neumann et al use two strains of *Escherichia coli*, one with a *gyrA-lacZ* fusion construct and another with a *gyrB-lacZ* fusion construct. Thus, Neumann et al provide a bacterial cell having a reporter gene under the control of two candidate regulatory sequences, i.e. those of gyrases A and B (see entire document, especially the paragraph bridging pp 55-56, as well as Table 1 on p. 54). Neumann et al the select two target essential proteins (gyrase A and gyrase B) and alter their synthesis by growing the *E. coli* under anaerobic conditions which are known to induce gyrase synthesis (see p. 58, first paragraph). Neumann et al teach monitoring expression of the reporter genes and determining thereby whether the candidate regulatory sequences are affected by a feedback mechanism responsive to

alteration of the synthesis or activity of the essential protein when they observe that under normal conditions the colonies of the recombinant *E. coli* strains are white, but "under anaerobic growth conditions the same bacteria exhibit a Lac+ phenotype showing deep red colonies due to enhanced expression of the respective LacZ fusion protein" (ibid). Similarly, Neumann et al teach a method of identifying a regulatory sequence whose activity is affected by an alteration of the synthesis or activity of an essential bacterial protein comprising monitoring the expression of a bacterial gene in a bacterial host through changes in beta-galactosidase activity under normal (aerobic culture conditions) and altered (anaerobic culture conditions) synthesis or activity of the essential protein (gyrase), identifying differential gene expression in the presence of normal and altered synthesis of gyrase (colonies are white under aerobic conditions and red under anaerobic conditions), and identifying thereby regulatory sequences affected by the feedback mechanism. Neumann et al further teach a method for identifying a modulator of a bacterial essential protein. Neumann et al teach providing an *E. coli* host cell which expresses the essential protein (gyrase), wherein the cell comprises a polynucleotide construct comprising a regulatory sequence operably linked to a reporter nucleic acid sequence

(*gyrA-lacZ* and *gyrB-lacZ*), wherein the regulatory sequence is associated with a feedback mechanism responsive to alteration in the synthesis or activity of the essential protein and identified according to the method of Neumann et al recited above. Neumann et al further teach contacting a test substance (various gyrase inhibitors) with the host cell and monitoring expression of the reporter gene to determine thereby whether said substance modulates the synthesis or activity of the essential protein (see especially Figures 2 and 3, as well as the paragraph bridging pp. 58-59). Neumann et al further teach such a method wherein the essential protein is involved in DNA replication since gyrase is involved in DNA replication and wherein inhibition of the essential protein up-regulates expression of the reporter nucleic acid sequence from the regulatory sequence and further wherein the regulatory sequence has the activity of a promoter for the nucleic acid sequence encoding the essential protein and inhibition of the essential protein up-regulates expression from its promoter (see Figure 2A-2B as well as Figure 3B on pages 60-61 and 63, respectively). Neumann et al further teach such a method wherein the reporter gene comprises a nucleic acid sequence which is up-regulated in response to alterations in the synthesis or activity of the essential protein, and wherein step (iii) comprises monitoring

for differential expression of the gene in the presence or absence of the test substance. Neumann et al also teach such a method further comprising determining whether the test substance demonstrates specific inhibition of the essential protein by determining the effect of gyrase inhibitors on DNA supercoiling (p. 59 and Figures 4-5 on pages 64-65).

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at (800) 786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter A. Schlapkohl whose telephone number is

(571) 272-4439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office.)

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

January 19, 2006

JAMES KETTER
PRIMARY EXAMINER